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An Approach Toward Homocalystegines and Silyl-homocalystegines. Acid-Mediated Migrations of Acetates in Seven-Membered Ring Systems

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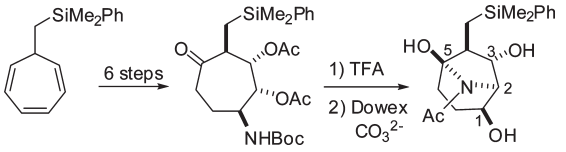
Received October 1, 2010



A short access to homocalystegine analogues silylated at C7 is described. The synthesis involves the desymmetrization of a (phenyldimethylsilyl)methylcycloheptatriene using osmium-mediated dihydroxylation, followed by the diol protection and a cycloaddition involving the remaining diene moiety and an acylnitroso reagent. Additions of the osmium and acylnitroso reagents were shown, through X-ray diffraction studies of the resulting major isomers, to occur *anti* and *syn*, respectively, relative to the $SiCH_2$ substituent. N−O bond cleavage on the resulting cycloadduct then produces the aminopolyol having a silylmethyl substituent. Oxidation of the C−Si bond also afforded an access to unusual amino-heptitols having five contiguous stereogenic centers. In the course of this work, we finally observed a unusual rearrangement taking place on cycloheptanone **18** substituted by two acetyl groups and a neighboring Boc-protected amine. A profound reorganization of the substituents on the seven-membered ring effectively took place under acidic conditions (TFA) leading to the thermodynamically more stable homocalystegine-type compound. DFT calculations of the conformational energy of isomeric silyl homocalystegines indicated that the product observed upon the acid-mediated rearrangement was the most stable of a series of analogues with various distributions of substituents along the seven-membered ring backbone. A tentative mechanism is proposed to rationalize the acetate migrations and inversions of the stereochemistry at various stereocenters.

Introduction

Calystegines are secondary metabolites isolated for the first time in 1988 from *Calystegia sepium*;[1] 26 different members of this class of alkaloids have been isolated so far.[2] They possess a polyhydroxylated nortropane skeleton and exhibit specific glycosidase (glucosidase and galactosidase) inhibitory activities.[3] Interestingly, whereas other iminosugars such as castanospermine **1** and swainsonine **2** (Figure 1) have been the subjects of numerous reports for their biological activities,[4] calystegines have attracted much less attention. However, these alkaloids enjoy an unusual polyhydroxylated bicyclic skeleton, and interesting biological activities probably lie hidden as shown by the recent report by Asano et al., who showed that calystegines A_3 (**3**), B_1 (**4**), B_2 (**5**), and C_1 (**6**) are potent lead compounds for Gaucher disease.[5] Various elegant approaches have been devised,[6] starting from sugar precursors,[7] using for instance ring-closing metathesis to generate the seven-membered ring.[8] Other strategies were based on the stereocontrolled introduction of the required substituents on cycloheptane building blocks.[9] As shown previously, we have recently initiated a study on a novel approach to calystegines and analogues relying on the

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(2) (a) Goldmann, A.; Milat, M. L.; Ducrot, P. H.; Lallemand, J. Y.; Maille, M.; Lepingle, A.; Charpin, I.; Tepfer, D. *Phytochemistry* **1990**, *29*, 2125–2127. (b) Dragger, B. *Nat. Prod. Rep.* **2004**, *21*, 211–223. (c) Watson, A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295. (d) Biastoff, S.; Dräger, B. *Alkaloids* **2007**, *64*, 49–102. (e) Asano, N. *Glycoscience* **2008**, 1887–1911.

DOI: 10.1021/jo101945h Published on Web 01/11/2011

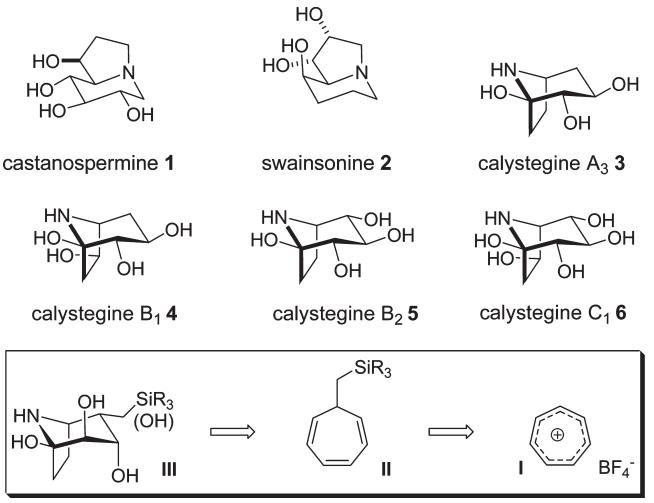

FIGURE 1. Calystegines and analogues.

desymmetrization of silyl-cycloheptatrienes, starting from commercially available tropylium salts.[10] Various silyl-metal complexes can be added that generate 7-silylcycloheptatrienes in good yield.[11] Interestingly, this approach offers an entry to calystegines having hydroxyl substituents both on the five- and six-membered rings, by the suitable functionalization of the three double bonds of cycloheptatriene. The silicon group both used is to differentiate the diastereotopic faces of the triene framework and may be oxidized[12] later in the sequence to afford an additional hydroxyl group. For biological activity screening purposes, it may also be interesting to keep the silicon group in the final target as this lipophilic group has been shown recently to enhance the activity in certain cases.[13] We report here the extension of the above approach to the synthesis and desymmetrization of 7-silylmethylcycloheptatrienes such as **II** and their subsequent elaboration. Compound **II** is available from the tropylium salt **I** and can be functionalized into calystegine analogue **III** using osmium-mediated dihydroxylation and acyl-nitroso cycloaddition, these processes allowing the incorporation of the OH and NH_2 substituents. In the course of these investigations, we also observed an intriguing rearrangement that has not, to our knowledge, been described so far. A complete description on the elaboration of **II** and a tentative mechanism of the rearrangement is proposed below.

Results and Discussion

The study started with the synthesis of (phenyldimethylsilyl)-methylcycloheptatriene **7**, obtained in a reasonable yield through treatment of tropylium tetrafluoroborate with the suitable Grignard reagent (Scheme 1).[11] Dihydroxylation of **7** using K_2OsO_4 dihydrate as an osmium source and $K_3Fe(CN)_6$ as a reoxidant[14] led to a separable mixture of diol **8** and hydroxyketone **9**. The latter is likely the result of an overoxidation of the osmate intermediate in the medium, a well-known reaction observed with other metals, including Mn and Ru.[15] The overall yield of the dihydroxylation was found to be less than that observed for the

SCHEME 1. Synthesis and Dihydroxylation of 7

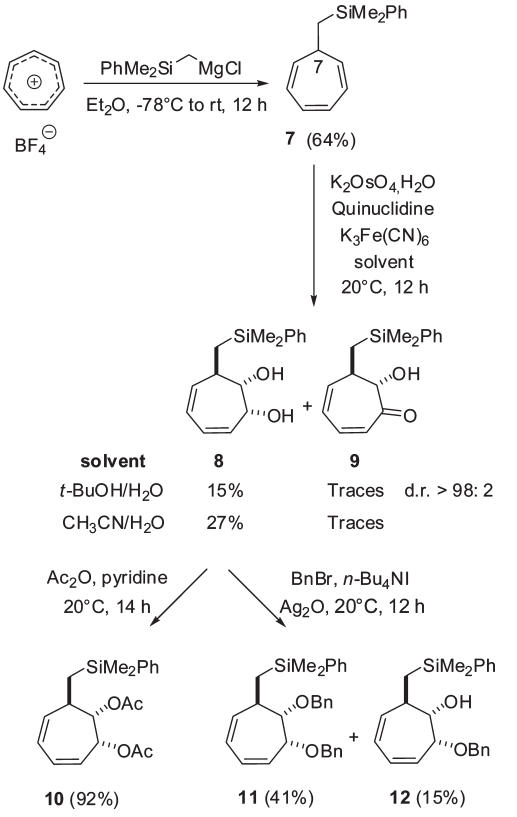

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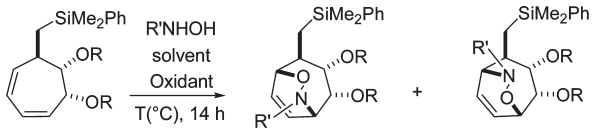
TABLE 1. Cycloaddition Reactions between 10 and 11 and Acylnitroso Reagents



10, R = OAc
11, R = Bn

13a, R = Ac, R' = Boc
14a, R = Bn, R' = Boc
15a, R = Bn, R' = Cbz

13b, R = Ac, R' = Boc
14b, R = Bn, R' = Boc
15b, R = Bn, R' = Cbz

entry	diene	oxidant	solvent	product	a/b ratio[e]	yield (%)[g]
1	**10**	*n*-Bu_4NIO_4[a]	CH_2Cl_2/MeOH3:1[c]	**13a/13b**	2:1[f]	52
2	**10**	$NaIO_4$[b]	MeOH/H_2O3:1[c]	**13a/13b**	3:2	73
3	**10**	$NaIO_4$[b]	MeOH/H_2O3:1[d]	**13a/13b**	5:4	66
4	**11**	$NaIO_4$[b]	MeOH/H_2O3:1[c]	**14a/14b**	16:1	56
5	**11**	$NaIO_4$[b]	MeOH/H_2O3:1[c]	**15a/15b**	15:1	57

[a]10 equiv of oxidant and hydroxylamine were used. [b]3 equiv of oxidant and hydroxylamine were used. [c]T = 20 °C. [d]T = 40 °C. [e]Ratio of isolated isomers. [f]10% of a third isomer was isolated, which structure could not be determined. [g]Combined isolated yields of both isomers.

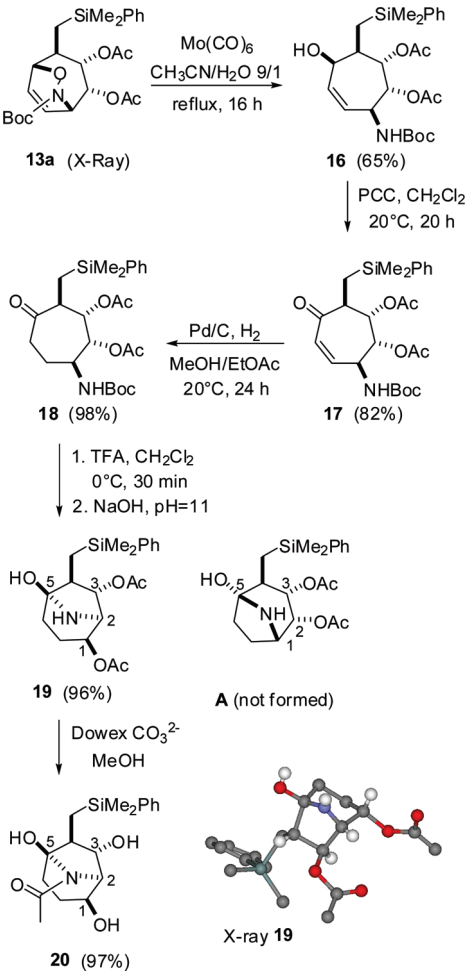
silylcyclohexadiene analogue,[16] probably due to some conformational effects. In contrast, the silylmethyl group was found to be very efficient at differentiating the two diastereotopic faces, the osmium reagent approaching *anti* relative to the silyl group (vide infra, X-ray diffraction studies on **13a**). The diastereocontrol was estimated to be complete by ^{1}H NMR studies. An enantioselective version of this reaction was also performed using Sharpless chiral ligands. Diol **8** with up to 63% enantiomeric excess was thus obtained using $(DHQD)_2PYR$ as a chiral ligand. However, because of this low enantiocontrol, the remaining part of the study was carried out and described in racemic series using achiral quinuclidine as a ligand. Protection of the diol as a bisacetate led to **10** in good yield. It is important to notice that performing the reaction via a three-step sequence without purification of intermediates **7** and **8** led to exactly the same overall yield. The hydroxyl groups were also protected as benzyl ethers, but in this case, yields were modest, the reaction leaving a large amount of monobenzylated product **12**.

With cycloheptadienes **10** and **11** in hand, a cycloaddition, involving the diene moiety of **10** and **11** and an acyl-nitroso reagent generated in situ, was performed to introduce the required amino and hydroxyl groups.[17] The regio- and diastereocontrol were studied varying the nature of the precursor, the solvent, and the oxidant. The results are summarized in Table 1.

The reaction led in most cases to two regioisomers as single diastereomers that could be separated through chromatography. Moderate to good regiocontrol was observed, depending on the nature of the protective groups, the benzylated precursor leading to higher differentiation. The large amount of oxidant and hydroxylamine generally required may be explained by the low reactivity of dienes **10**−**11**. The regio- and diastereoselectivity of the cycloaddition on diacetate **10** was established unambiguously through X-ray structure determination of the regioisomer **13a**. The same topicity was assumed for the dibenzylated analogue **11**. The formation of **13a**−**15a** as major regioisomers may be rationalized invoking steric interactions between the bulky carbamate and the silylmethyl groups. As observed in the silylcycloheptatrienes series,[10] the approach of the nitroso reagent occurred *syn* to the silylmethyl substituent.

Although benzylated diene **11** led to better regiocontrol, the further elaboration of the cycloadduct was continued with bis-acetate **13a** more easily available on larger scale. Cleavage of the N−O bond was thus performed using $Mo(CO)_6$ in CH_3CN/H_2O mixture (use of SmI_2 in THF gave similar results), leading to Boc-protected amino-alcohol **16** in good yield. The five-membered nitrogen ring found in

SCHEME 2. Elaboration of 13a and Synthesis of Silyl-calystegine 20



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(15) (a) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123–7125. (b) Plietker, B. *Org. Lett.* **2004**, *6*, 289–291. (c) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116–1124. (d) Plietker, B.; Niggemann, M. *Org. Biomol. Chem.* **2004**, *2*, 2403–2407.
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calystegines was then elaborated through oxidation of the unprotected alcohol with PCC, followed by hydrogenation of the double bond, leading to ketone **18** in 81% over two steps. Removal of the Boc group under acidic conditions was supposed to provide the corresponding calystegine-type structure **A**, but surprisingly, X-ray diffraction studies of crystals issued from the Boc deprotection led to structure **19**, in which an acetate (at C2) and the amino group (at C1) had migrated. Efforts were made to perform the deprotection of the unexpected calystegine analogue **19**. Mild basic conditions last provided the acetamide **20** in quantitative yield. Unfortunately and regardless of the conditions used, it was impossible in our hands to cleave efficiently the acetamide moiety to provide the free amine. The rearrangement observed in the sequence depicted in Scheme 2 is puzzling, and it was not clear in which step it occurred. Reasoning that the hydrogenation step in the presence of palladium catalysts might be at the origin of the rearrangement due to π-allyl-palladium complexes formed during the reaction, it was decided to repeat the whole sequence, changing the order of the steps. The new sequence of reactions is depicted in Scheme 3 below. Diacetate **13a** was thus hydrogenated to provide the saturated analogue **21** in nearly quantitative yield. N−O bond cleavage with SmI_2 led to the protected amino-alcohol **22**, which was then oxidized with PCC, affording the *N*-protected aminoketone **18**, identical in many respect with that formed by the sequence depicted in Scheme 2. Boc deprotection of **18** with TFA led as before to the rearranged product **19** in 86% yield. In our efforts to reach homocalystegine analogues, we also attempted the oxidation of the C−Si bond. Using standard Fleming conditions,[12] oxidation of **18** afforded the α-bromoketone **23**, which structure was unambiguously assigned through X-ray diffraction studies. Bromination occurs before or after the C−Si bond oxidation, through reaction between the enol form of ketone **18** and bromine issued from the reaction of KBr and AcOOH under acidic conditions. Finally, from the structure of **23**, it can be deduced that **18** has not been rearranged during the sequence in Scheme 3, implying that the rearrangement does take place during Boc deprotection under acidic conditions (TFA).

The rather mild conditions used for the deprotection of the Boc protecting group imply that a strong driving force operates during the rearrangement. Seven-membered rings are known to be flexible, and acetates are well-known to migrate from one position to another, for instance in sugars. We therefore envisioned that a thermodynamically driven pathway might lead to the rearranged

SCHEME 3. Second Approach to the Synthesis of Silyl-calystegine 19

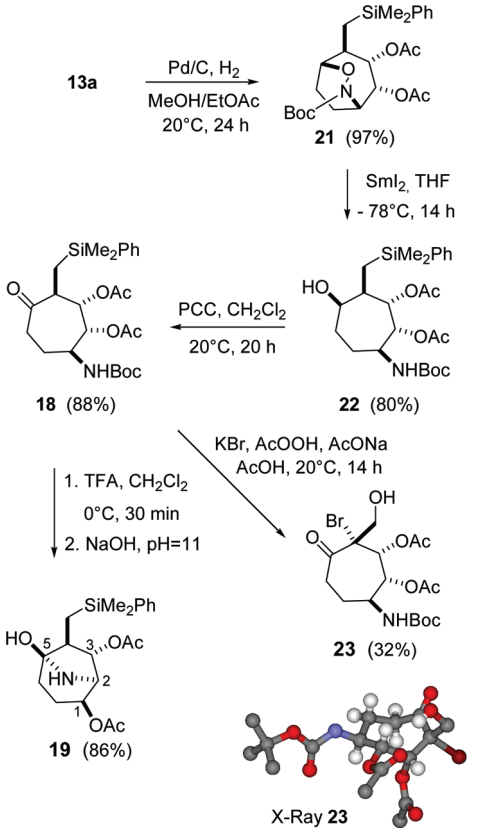
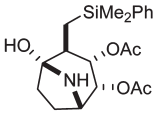
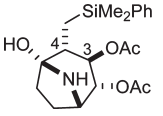
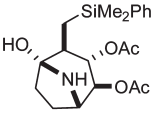
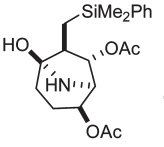
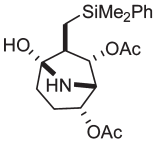
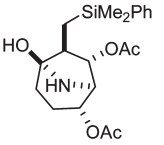
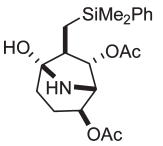


TABLE 2. DFT Calculations (B3LYP-6-31G(d)) of the Conformational Energy of Isomeric Silylcalystegines

Entry	Isomer	Energy (kcal/mol)
1	 **A**	15.7
2	 **A'**	-3.8
3		14.8
4	 **19**	0
5	 **B**	11.2
6		11.9
7		12.2

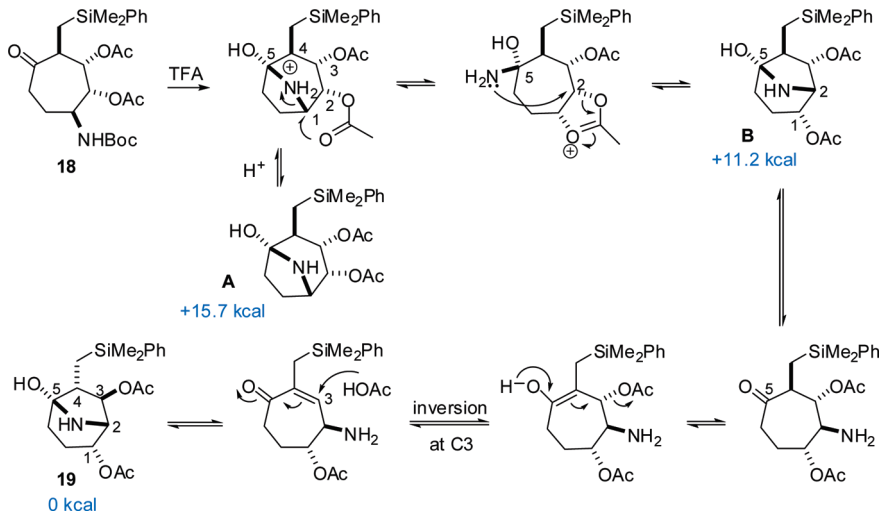


FIGURE 2. Mechanism of the rearrangement of Boc-protected amino-ketone **18**.

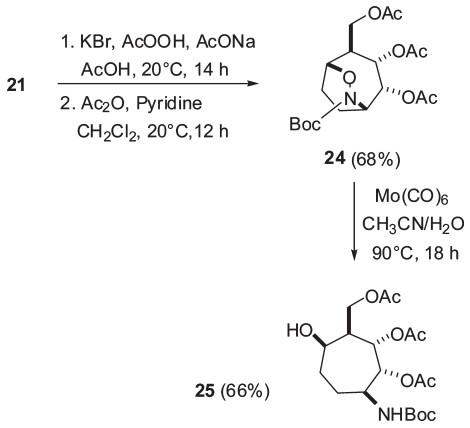
structure **19** through a succession of acetate migrations and aminal ring opening. DFT calculations (B3LYP-6-31G(d)) were thus carried out to estimate the ground state energy of the various isomers of **19** and the expected product **A** (Scheme 2). As the number of stereoisomers is very high, considering the number of stereogenic centers, we considered in the calculations only isomers in which the relative configuration between C3 and C4 is *trans* for steric reasons. The results summarized in Table 2 indicate that the expected product **A** (entry 1) exhibits a relatively high conformational energy of 15.7 kcal/mol relative to the rearranged product **19** (entry 4), which is effectively the most stable isomer in this series.

On the basis of these calculations, we propose below a tentative mechanism for the rearrangement (Figure 2), which should involve the removal of the Boc group and then the protonation of the nitrogen of the aminal, followed by the migration of the acetate from the C2 to the C1 center. This migration would then be followed by the inversion of the configuration at C3 through an acid-mediated retro-Michael−Michael process,[18] leading to the more stable silyl-calystegine **19**. This mechanism thus involves two important events: (1) the acetate migration from C1 to C2 and (2) the epimerization at C3 and C4. We could also consider that these two events may be inverted, the epimerization occurring first. This pathway was however ruled out by calculating the conformational energy of **A′** (Table 2, entry 2), an epimer of **A** (at C3 and C4). The energy of **A′** was found to be lower by nearly 4 kcal/mol relative to the other isomers, implying that if epimerization at C3 and C4 from **18** occurred first, then **A′** would likely be the only product of the reaction. Allowing for the fact that only 3,4-*trans* product was formed, 3,4-*cis* isomers energies were not calculated.

This rearrangement thus leads to an unusual type of calystegines having a fully functionalized five-membered ring starting from the readily available cycloheptane aminodiol **18**. In parallel, we have developed a straightforward route to the penta-substituted aminocycloheptitol **25** starting from

(18) Retro-Michael processes have been observed during our studies on closely related ketones, with the loss of the acetate and formation of the α,β-unsaturated ketone.

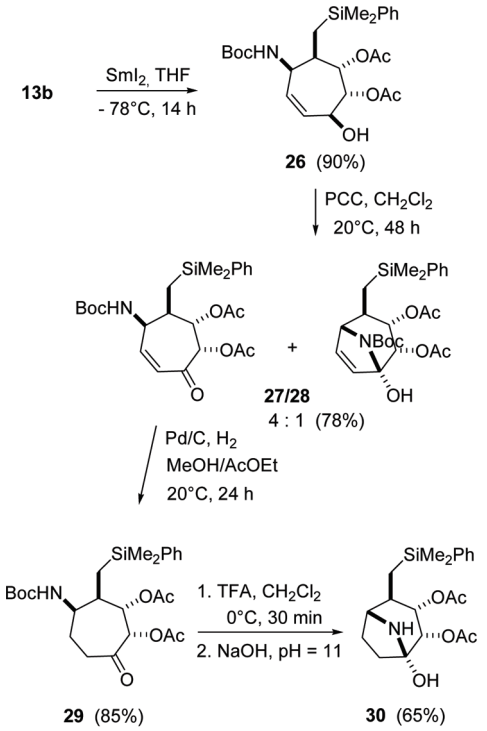
SCHEME 4. Synthesis of Protected Amino-heptitol 25

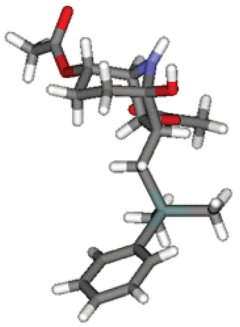


diacetate **21**, through the sequence depicted in Scheme 4. This involves a C−Si bond oxidation, followed by the protection of the hydroxyl group as an acetate, which provided triacetate **24** in 68% overall yield. The N−O bond cleavage using $Mo(CO)_6$ (which is easier to handle than SmI_2) finally afforded the expected hydroxycarbamate **25**. Our efforts to oxidize the free alcohol function unfortunately led to an inseparable mixture of the desired ketone and the corresponding unsaturated ketone resulting from the β-elimination of the exocyclic acetate. This last observation supports our hypothesis of a retro-Michael−Michael process occurring during the transformation of **18** into **19** (Scheme 3 and Figure 2).

As discussed above, nitroso cycloaddition led, under some conditions, to large amount of the regioisomeric cycloadducts **13b**, **14b**, and **15b** (Table 1), which might also be valuable intermediates en route for the synthesis of unusual calystegines. Compound **13b** was thus further functionalized following the strategy described for the other regioisomer. N−O bond cleavage of cycloadduct **13b** led to the allylic alcohol **26**, oxidation of which using PCC provided a 4:1 mixture of the unsaturated ketone **27** and the corresponding Boc-protected aminal **28**. Hydrogenation of the double bond in **27** and removal of the Boc group with trifluoroacetic acid finally afforded the silyl-calystegine **30** in 34% overall yield from **13b**.

SCHEME 5. Synthesis of Silyl-calystegine 30





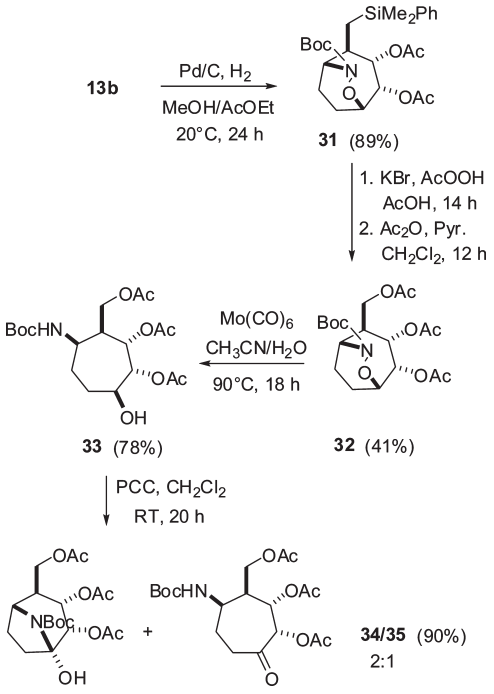
X-ray **30**

The structure of **30** exhibits all substituents on both rings in equatorial position as shown by X-ray diffraction studies (Scheme 5).

As above, the silyl group may also be oxidized to provide the corresponding aminocycloheptitol, then the unnatural calystegine. Hydrogenation of the double bond of regioisomer **13b** prior to the oxidation of the C−Si bond provided, after protection of the alcohol as an acetate, the bicyclic skeleton of **31**, and reduction of the N−O bond with $Mo(CO)_6$ led to pentasubstituted heptitol **33** in reasonable yields (Scheme 6). PCC oxidation of the free alcohol function finally provided the unnatural protected calystegine **34**, along with its open ketone form **35** in 26% overall yield from **13b**. Compounds **34** and **35** were obtained as an inseparable mixture, and their ratio was estimated from the ^{1}H NMR spectra of the crude product.

In summary, we have disclosed here our recent studies on the desymmetrization and functionalization of silylmethylcycloheptatrienes as a route to silyl-homocalystegines and homocalystegines. These compounds can be obtained in 7 and 8 steps, respectively, from commercially available tropylium

SCHEME 6. Synthesis of Protected Calystegine 34



salt. In the course of our investigations, we have encountered an unexpected rearrangement, likely resulting from a thermodynamically driven intra- and intermolecular acetate group migration.

Experimental Section

7-((Dimethyl(phenyl)silyl)methyl)cyclohepta-3,5-diene-1,2-diyl Diacetate (10). To a solution of **8** (300 mg, 1.09 mmol, 1 equiv) in CH_2Cl_2 (7 mL) were added pyridine (345 mg, 4.36 mmol, 4 equiv), a small amount of DMAP, and acetic anhydride (670 mg, 6.54 mmol, 6 equiv) at 20 °C. The resulting mixture was stirred for 14 h at room temperature, poured into saturated NH_4Cl_{aq} (20 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuum. The crude residue was purified by silica gel column chromatography (petroleum ether/AcOEt: 90/10) to provide **10** as a colorless oil (360 mg, 92%). R_f = 0.4 (petroleum ether/EtOAc: 90/10). IR (film, NaCl): ν 3417, 2955, 2899, 1745, 1732, 1427, 1371, 1229, 1113, 1027, 837, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.59−7.47 (m, 2H), 7.42−7.30 (m, 3H), 6.01−5.87 (m, 1H), 5.84−5.72 (m, 1H), 5.68−5.55 (m, 3H), 5.29−5.20 (m, 1H), 2.69−2.56 (m, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.07 (dd, J = 14.7, 4.5 Hz, 1H), 0.92 (dd, J = 14.7, 10.2 Hz, 1H), 0.37 (s, 3H), 0.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 170.4, 170.1, 138.6, 136.1, 133.6, 129.1, 128.8, 128.0, 125.3, 123.4, 77.7, 71.4, 38.3, 21.6, 21.1, 21.0, −2.1, −2.3. HRMS (ESI): $[M + Na]^+$ $C_{20}H_{26}O_4SiNa$ calcd 381.1498, found 381.1506.

Acyl Nitroso Cycloaddition General Procedure. Method A. *n*-Bu_4NIO_4 (3−10 equiv), RNHOH (3−10 equiv), in CH_2Cl_2/MeOH (3/1). Silylcycloheptadienes **10** (1 mmol) and *n*-Bu_4NIO_4 (3−10 mmol) were dissolved in a 3/1 mixture of CH_2Cl_2/MeOH (0.1 M), and BocNHOH (3−10 mmol) in CH_2Cl_2 (10−20 mL) was added dropwise during 2 h. The resulting solution was stirred for 12 h at 20 °C and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated brine and dried

over anhydrous Na_2SO_4, and the solvents were concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/EtOAc: 95/15 to 80/20)) affording the cycloadducts **13a** and **13b**.

Method B. $NaIO_4$ (3 equiv), RNHOH (3 equiv), in MeOH/H_2O (3/1). Silylcycloheptadienes **10** (1 mmol) and $NaIO_4$ (3 mmol) were dissolved in a 3/1 mixture of MeOH/H_2O (0.1 M), and BocNHOH (3 mmol) in MeOH was added dropwise. The resulting solution was stirred for 12 h at 20 °C and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvents were concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/EtOAc (95/15 to 80/20)) affording the cycloadducts **13a** and **13b**.

7-(*tert*-Butoxycarbonyl)-4-((dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-2,3-diyl Diacetate (13a). $R_f = 0.15$ (petroleum ether/EtOAc: 85/15). Mp = 135−137 °C (EtOAc). IR (solid, KBr): ν 3584, 2955, 2360, 1747, 1371, 1368, 1242, 836 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56−7.46 (m, 2H), 7.41−7.33 (m, 3H), 6.22 (t, J = 8.9 Hz, J = 7.3 Hz, 1H), 6.11 (t, J = 7 Hz, J = 8 Hz, 1H), 5.46−5.43 (m, 1H), 5.27−5.21 (m, 1H), 4.97 (t, J = 6.7 Hz, J = 6.3 Hz, 1H), 4.27 (d, J = 6.7 Hz, 1H), 2.10−2.01 (m, 1H), 2.05 (s, 3H), 1.99 (s, 3H), 1.47 (s, 9H), 1.20−1.09 (m, 1H), 0.96−0.87 (m, 1H), 0.35 (s, 3H), 0.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.75 MHz): δ (ppm) 169.9, 155.5, 138.3, 133.7, 131.5, 129.3, 128.0, 127.6, 82.5, 76.8, 74.7, 69.7, 53.2, 39.9, 28.2, 20.9, 17.4, −2.4. HRMS (ESI): $[M + Na]^+$ $C_{25}H_{35}NO_7SiNa$ calcd 512.2147, found 512.2149.

7-(*tert*-Butoxycarbonyl)-2-(dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-3,4-diyl Diacetate (13b). $R_f = 0.13$ (petroleum ether/EtOAc: 85:15). Mp = 146−148 °C (EtOAc). IR (solid, KBr): ν 3585, 2957, 2362, 1747, 1374, 1368, 1246, 838 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.56−7.48 (m, 2H), 7.41−7.32 (m, 3H), 6.28 (t, J = 8.3 Hz, 1H), 6.11−6.03 (m, 1H), 5.38−5.27 (m, 2H), 4.87 (t, J = 6.4 Hz, 1H), 4.52 (d, J = 7.5 Hz, 1H), 2.09−2.00 (m, 4H), 1.96 (s, 3H), 1.05 (AB system, J_{AB} = 10.7 Hz, 1H), 0.85 (AB system, J_{AB} = 14.8 Hz, 1H), 0.37 (s, 3H), 0.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 170.0, 169.8, 157.0, 138.3, 133.8, 132.7, 129.3, 128.0, 126.6, 82.3, 75.0, 71.8, 57.2, 37.2, 28.3, 20.9, 20.8, −2.0, −2.6. MS (ESI) m/z (%): 512 $[M + Na]^+$ (12), 456 $[M + Na - (C_4H_8)]^+$ (100), 412 $[M + Na - Boc]^+$ (5). HRMS (ESI): $[M + Na]^+$ $C_{25}H_{35}NO_7SiNa$ calcd 512.2147, found 512.2149.

Benzyl 2,3-Bis(benzyloxy)-4-((dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (15a) and Benzyl 3,4-Bis(benzyloxy)-2-((dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (15b). Silylcycloheptadiene **11** (374 mg, 0.823 mmol, 1 equiv) and $NaIO_4$ (706 mg, 3.293 mmol, 4 equiv) were dissolved in a 2/1 mixture of MeOH/H_2O (6/3), and CbzNHOH (412 mg, 2.469 mmol, 3 equiv) in MeOH was added dropwise during 2 h. The resulting solution was stirred for 12 h at 20 °C and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. (30 mL) The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4, and the solvents concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/EtOAc: 90/10) affording a 18/1 mixture of **15a/15b** (273 mg of **15a** (54%), 18 mg of **15b** (3%)).

Benzyl 2,3-Bis(benzyloxy)-4-((dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (15a). $R_f = 0.25$ (petroleum ether/EtOAc: 85/15). IR (film, NaCl): ν 2952, 1703, 1454, 1261, 1112, 1072, 834 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.55−7.49 (m, 2H), 7.42−7.27 (m, 20H), 6.27 (t, J = 7.6 Hz, J = 8.6 Hz, 1H), 6.12 (t, J = 7.2 Hz, J = 8.5 Hz, 1H), 5.25−5.14 (m, 2H), 5.06−4.95 (m, 1H), 4.68−4.53 (m, 3H), 4.42 (d, J_{AB} = 11.6 Hz, 1H), 4.26 (d, J = 6.6 Hz, 1H), 4.11 (dd, J = 4.2, 6.6 Hz, 1H), 3.66 (dd, J = 4.0, 8.4 Hz, 1H), 2.23−2.13 (m, 1H), 1.28−1.21 (m, 1H), 1.09−0.99 (m, 1H), 0.33 (s, 3H), 0.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.75 MHz): δ (ppm) 155.9, 138.8, 138.5, 138.3, 136.0, 133.8, 131.0, 129.2, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.87, 127.84, 127.55, 127.5, 83.1, 78.2, 75.0, 72.7, 72.6, 68.0, 53.3, 40.7, 17.3, −2.2, −2.4. MS (ESI) m/z (%): 620 $[M + H]^+$ (100), 452 $[M + H - (CbzNHOH)]$ (39). HRMS (ESI): $[M + H]^+C_{38}H_{41}NO_5Si$ calcd 620.2826, found 620.2849.

Benzyl 3,4-Bis(benzyloxy)-2-((dimethyl(phenyl)silyl)methyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (15b). $R_f = 0.22$ (petroleum ether/EtOAc: 85/15). IR (film, NaCl): ν 3373, 2970, 1714, 1454, 1250, 1111, 1072, 1045, 831 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.60−7.49 (m, 2H), 7.48−7.37 (m, 20H), 6.27−6.25 (m, 2H), 5.28−5.27 (m, 2H), 4.81−4.77 (m, 3H), 4.74−4.57 (m, 3H), 4.23 (dd, J = 7.0, 4.2 Hz, 1H), 3.90−3.85 (m, 1H), 2.28−2.23 (m, 1H), 1.41−1.33 (m, 1H), 1.02−0.96 (m, 1H), 0.42 (s, 6H). ^{13}C NMR ($CDCl_3$, 100.75 MHz): δ (ppm) 158.0, 138.9, 138.7, 138.6, 136.1, 134.0, 131.3, 129.3, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 83.6, 76.0, 73.5, 73.1, 72.8, 68.1, 57.1, 38.6, 17.2, −2.0, −2.4. MS (ESI) m/z (%): 620 $[M + H]^+$ (20), 452 $[M + H - (CbzNHOH)]$ (55). HRMS (ESI): $[M + H]^+C_{38}H_{41}NO_5Si$ calcd 620.2826, found 620.2834.

3-(*tert*-Butoxycarbonylamino)-7-((dimethyl(phenyl)silyl)methyl)-6-hydroxycyclohept-4-ene-1,2-diyl Diacetate (16). A mixture of **13a** (480 mg, 0.981 mmol, 1 equiv), $Mo(CO)_6$ (285 mg, 1.08 mmol, 1.1 equiv), 10.8 mL of acetonitrile, and 1.2 mL of water was heated under reflux during 16 h and allowed to cool to room temperature. Then 2 g of silica gel and EtOAc (10 mL) were then added to the mixture, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc: 70/30) affording **16** as a colorless oil (310 mg, 65%). $R_f = 0.1$ (petroleum ether/EtOAc 70:30). IR (film, NaCl): ν 3556, 2975, 2360, 1745, 1697, 1367, 1249, 1166, 1034, 836 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56−7.48 (m, 2H), 7.38−7.30 (m, 3H), 5.61−5.52 (m, 1H), 5.49−5.39 (m, 1H), 5.22−5.14 (m, 1H), 4.94−4.85 (m, 1H), 4.82−4.63 (m, 3H), 2.14 (br s, 4H), 1.93 (s, 3H), 1.61−1.53 (m, 2H), 1.45 (s, 9H), 1.12 (dd, J = 5.2, 15.1 Hz, 1H), 0.80 (dd, J = 9.7, 15.3 Hz, 1H), 0.36 (s, 3H), 0.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.8, 170.1, 155.4, 138.8, 136.1, 133.8, 130.0, 129.2, 128.1, 79.8, 74.6, 68.5, 48.7, 44.3, 28.5, 21.3, 20.9, 12.3, −2.4, −2.5. MS (ESI) m/z (%): 514 $[M + Na]^+$ (100). HRMS (ESI): $[M + Na]^+$ $C_{25}H_{37}NO_7SiNa$ calcd 514.2237, found 514.2237.

3-(*tert*-Butoxycarbonylamino)-7-((dimethyl(phenyl)silyl)methyl)-6-oxocyclohept-4-ene-1,2-diyl Diacetate (17). To a stirred solution of **16** (300 mg, 0.61 mmol, 1 equiv) in dry dichloromethane (7 mL), under nitrogen at 20 °C, was added 4 Å molecular sieves (350 mg, crushed). PCC (0.262 g, 1.098 mmol, 1.8 equiv) was then added, and the resulting suspension was stirred for 20 h. Diethyl ether (10 mL) was added, and the slurry was filtered through a pad of silica gel. The solvent was removed under reduced pressure, and the crude residue was then purified by silica gel column chromatography (petroleum ether/EtOAc: 80/20) to provide **17** (246 mg, 82%) as a colorless oil. $R_f = 0.6$ (petroleum ether/EtOAc: 70/30). IR (film, NaCl): ν 3556, 2975, 2341, 1743, 1653, 1558, 1371, 1237, 680 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.51−7.42 (m, 2H), 7.38−7.29 (m, 3H), 6.16 (d, J = 12.9 Hz, 1H), 5.80 (d, J = 13.1 Hz, 1H), 5.36 (d, J = 9.1 Hz, 1H), 5.14 (d, J = 5.5 Hz, 1H), 4.95−4.70 (m, 2H), 2.95−2.84 (m, 1H), 2.05 (s, 3H), 1.99 (s, 3H), 1.42 (s, 9H), 1.29−1.15 (m, 1H), 1.12−1.00 (m, 1H), 0.31 (s, 3H), 0.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 201.0, 170.4, 170.1, 155.2, 141.4, 137.7, 133.8, 129.7, 129.3, 128.0, 80.3, 74.2, 70.8, 51.8, 50.1, 28.4, 21.0, 20.9,

16.9, −2.6, −3.0. HRMS (ESI): $[M + Na]^+$ $C_{25}H_{35}NO_7SiNa$ calcd 512.2075, found 512.2070.

7-(*tert*-Butoxycarbonylamino)-3-((dimethyl(phenyl)silyl)methyl)-4-oxocycloheptane-1,2-diyl Diacetate (18). Compound **17** (230 mg, 0.47 mmol, 1 equiv) was dissolved in a mixture of methanol and ethyl acetate (2:1, 6 mL), and Pd/C 10 mol % (50 mg, 0.047 mmol, 0.1 equiv) was added. An inert atmosphere of H_2 was installed, and the reaction mixture was stirred at 20 °C for 24 h. The reaction mixture was filtered through a Celite pad and washed with ethyl acetate. The solvent was removed under reduced pressure, the crude residue (98% yield) was clean enough to be used in the further step without any purification. It was purified by silica gel column chromatography (petroleum ether/EtOAc: 80/20) to provide **18** (200 mg, 87%) as a colorless oil, which was fully characterized. $R_f = 0.2$ (petroleum ether/EtOAc 70:30). IR (film, NaCl): ν 3556, 2360, 1743, 1633, 1420, 1260, 1224, 1024, 799, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56−7.42 (m, 2H), 7.41−7.29 (m, 3H), 5.17−4.98 (m, 2H), 4.72 (d, J = 8.6 Hz, 1H), 4.09 (br s, 1H), 2.77−2.66 (m, 1H), 2.60−2.37 (m, 2H), 2.07 (s, 4H), 1.98 (s, 3H), 1.83−1.65 (m, 1H), 1.40 (s, 9H), 1.31−1.17 (m, 1H), 0.96 (dd, J = 6.5, 14.6 Hz, 1H), 0.33 (s, 3H), 0.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.75 MHz): δ (ppm) 210.8, 170.5, 169.8, 155.3, 138.0, 133.8, 129.3, 128.0, 79.9, 74.3, 73.0, 51.2, 50.0, 38.8, 28.4, 27.8, 21.1, 20.9, 16.3, −2.6, −2.9. MS (ESI) m/z (%): 514 $[M + Na]^+$ (7), 458 $[M + Na - (C_4H_8)]^+$ (100), 414 $[M + Na - (Boc)]^+$ (10). HRMS (ESI): $[M + Na]^+$ $C_{25}H_{37}NO_7SiNa$ calcd 514.2237, found 514.2234.

6-((Dimethyl(phenyl)silyl)methyl)-5-hydroxy-8-azabicyclo[3.2.1]octane-2,7-diyl Diacetate (19). At 0 °C, TFA (1.8 mL, 24.7 mmol, 135 equiv) was added to a solution of **18** (90 mg, 0.183 mmol, 1 equiv) in CH_2Cl_2 (9 mL), and the reaction mixture was stirred at this temperature for 30 min until reaction completion (TLC control). A 3 M NaOH solution was added until the pH remained basic (pH ≤ 11). The reaction mixture was then stirred at room temperature for 50 min. After separation of the two layers, the aqueous one was extracted with CH_2Cl_2 (2 × 20 mL).The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide **19** (70 mg, 96%) as a white solid. R_f = 0.1 (petroleum ether/EtOAc 20:80). Mp = 157−159 °C (EtOAc). IR (film, NaCl): ν 3353, 2956, 2360, 1736, 1654, 1540, 1248, 1155, 1025, 834, 667 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.54−7.46 (m, 2H), 7.39−7.30 (m, 3H), 6.59 (d, J = 6.0 Hz, 1H), 4.34 (d, J = 5.8 Hz, 1H), 3.95−3.84 (m, 2H), 2.38−2.26 (m, 2H), 2.01−1.87 (m, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.80−1.68 (m,1H), 1.32−1.19 (m,1H), 1.03 (dd, J = 3.5, 14.6 Hz, 1H), 0.97−0.86 (m, 1H), 0.34 (s, 3H), 0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.6, 170.8, 138.4, 133.5, 129.4, 128.0, 106.8, 81.0, 80.2, 49.0, 47.1, 29.9, 25.1, 23.4, 21.1, 12.9, −2.1, −3.4. HRMS (ESI): $[M + Na]^+$ $C_{20}H_{29}NO_5SiNa$ calcd 414.1712, found 414.1718. Anal. Calcd for $C_{20}H_{29}NO_5Si$ (391.18): C 61.35, H 7.47, N 3.58. Found: C 61.55, H 7.44, N 3.56.

1-(7-((Dimethyl(phenyl)silyl)methyl)-1,4,6-trihydroxy-8-azabicyclo[3.2.1]octan-8-yl)ethanone (20). To a solution of the acetate compound **19** (125 mg, 3.19 mmol) in methanol was added DOWEX CO_3^{2-} (2 spoons). The mixture was stirred overnight at room temperature. It was then filtered, and the resin was rinsed thoroughly with methanol. The crude material was obtained after evaporation and purification by silica gel column chromatography (CH_2Cl_2/MeOH: 90/10) provided **20** as a colorless solid (112 mg, 97%). R_f = 0.42 (CH_2Cl_2/MeOH: 90/10). Mp = 58−60 °C (EtOAc). IR (neat ATR): ν 3277, 2951, 1642, 1547, 1426, 1248, 1111, 1003, 828 cm^{-1}. ^1H NMR (CD_3OD, 200 MHz): δ (ppm) 7.65−7.49 (m, 2H), 7.38−7.23 (m, 3H), 4.00−3.72 (m, 3H), 2.15−1.20 (m, 6H), 1.93 (s, 3H), 0.94 (d, J = 7.8 Hz, 2H), 0.40 (s, 3H), 0.39 (s, 3H). ^{13}C NMR (CD_3OD, 75.5 MHz): (two rotamers are visible and are noted R1 and R2) δ (ppm) 172.4 (R1), 172.3 (R2), 133.3, 128.6, 127.6, 127.5, 106.7, 82.6, 76.4, 53.2, 46.6, 29.7, 23.3 (R1), 23.2 (R2), 21.4 (R1), 21.3 (R2), 12.7, −3.6, −4.0. HRMS (ESI): $[M + Na]^+$ $C_{18}H_{27}NO_4NaSi$ calcd 372.16071, found 372.1604.

3-Bromo-7-(*tert*-Butoxycarbonylamino)-3-(hydroxymethyl)-4-oxocycloheptane-1,2-diyl Diacetate (23). Peracetic acid (36−40% in AcOH, 0.8 mL) was added dropwise to a stirred mixture of **18** (120 mg, 0.24 mmol, 1 equiv) in acetic acid (0.5 mL) at 0 °C, and then potassium bromide (57 mg, 0.48 mmol, 2 equiv) and sodium acetate (79 mg, 0.96 mmol, 4 equiv) were also added. The mixture was allowed to warm to room temperature, and the mixture was stirred overnight. The mixture was quenched with aqueous sodium thiosulfate solution (25% (15 mL) at 0 °C, and the aqueous layer was saturated with NaCl. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium carbonate and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc: 65/35) to provide **23** (35 mg, 32%) as a yellow solid. R_f = 0.35 (petroleum ether/EtOAc: 60/40). Mp = 153−154 °C ($CHCl_3$). IR (film, NaCl): ν 1760, 1710, 1691, 1530, 1213, 1165, 1050, 813 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.69 (s, 1H), 5.17 (d, J = 10.3 Hz, 1H), 4.80−4.70 (m, 1H), 4.32 (dd, J = 6.7, 12 Hz, 1H), 4.30−4.16 (m, 1H), 4.02 (dd, J = 5.6, 12.1 Hz, 1H), 3.32 (brs, 1H), 3.13 (t, J = 12.7 Hz, 1H), 2.56 (t, J = 12.7 Hz, J = 12.3 Hz, 1H), 2.36−2.19 (m, 1H), 2.24 (s, 3H), 2.18−2.0 (m, 1H), 2.04 (s, 3H), 1.77 (br s, 1H), 1.65−1.35 (m, 1H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 203.3, 171.6, 169.3, 155.4, 80.0, 75.1, 73.3, 66.8, 66.4, 49.9, 37.6, 28.9, 28.4, 21.1, 21.0. MS (ESI) m/z (%): 474 $[M + Na]^+$ (100), 418 $[M + Na - (C_4H_8)]^+$ (24). HRMS (ESI): $[M + Na]^+$ $C_{17}H_{25}BrNO_8Na$ calcd 474.0733, found 474.0756.

4-(*tert*-Butoxycarbonylamino)-3-((dimethyl(phenyl)silyl)methyl)-7-oxocycloheptane-1,2-diyl Diacetate (29). Compound **27** (90 mg, 0.18 mmol, 1 equiv) was dissolved in a mixture of methanol and ethyl acetate (2:1, 2.5 mL), and then Pd/C 10% (19 mg, 0.018 mmol, 0.1 equiv) was added under N_2 atmosphere. An atmosphere of H_2 was installed, and the reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The solvent was removed under reduced pressure, and the crude residue was then purified by silica gel column chromatography (petroleum ether/EtOAc: 80/20) to provide **29** (75 mg, 80%) as a colorless oil. R_f = 0.4 (petroleum ether/EtOAc: 70/30). IR (film, NaCl): ν 3376, 2917, 1747, 1668, 1427, 1225, 1168, 910, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.59−7.49 (m, 2H), 7.40−7.30 (m, 3H), 5.44 (br s, 1H), 5.14−5.04 (m, 1H), 4.56−4.39 (m, 1H), 3.89−3.71 (m, 1H), 2.62−2.36 (m, 3H), 2.19−1.93 (m, 2H), 2.06 (s, 3H), 1.99 (s, 3H), 1.70−1.56 (m, 1H), 1.40 (s, 9H), 0.94−0.83 (m, 2H), 0.42 (s, 3H), 0.40−0.31 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 201.2, 169.9, 169.6, 154.7, 138.0, 133.6, 129.5, 128.2, 79.8, 75.5, 74.6, 50.9, 39.2, 38.6, 28.5, 23.4, 21.1, 20.7, 11.7, −2.7, −3.3. MS (ESI) m/z (%): 514 $[M + Na]^+$ (7), 458 $[M + Na - (C_4H_8)]^+$ (21), 414 $[M + Na - (Boc)]^+$ (14), 354 $[M - H - (SiMe_2Ph)]^+$ (100). HRMS (ESI): $[M + Na]^+$ $C_{25}H_{37}NO_7SiNa$ calcd 514.2237, found 514.2228.

4-((Dimethyl(phenyl)silyl)methyl)-1-hydroxy-8-azabicyclo[3.2.1]octane-2,3-diyl Diacetate (30). At 0 °C, TFA (1.12 mL, 15.12 mmol, 135 equiv) was added to a solution of **29** (55 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2 (5.5 mL), and the reaction mixture was stirred at this temperature until completion. A 3 M NaOH solution was added until pH remained basic (pH ≤ 11). The reaction mixture was then stirred at rt during 50 min. After separation of the two layers, the aqueous one was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/EtOAc: 20/80) to provide **30** (28 mg, 65%) as a white solid. R_f = 0.1 (petroleum ether/EtOAc 20:80).

Mp = 154−156 °C (EtOAc). IR (Solid, KBr): ν 3353, 2955, 2360, 1737, 1653, 1540, 1227, 1248, 1155, 1025, 834 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.53−7.46 (m, 2H), 7.38−7.31 (m, 3H), 5.16−5.06 (m, 2H), 3.13 (d, J = 7.5 Hz, 1H), 2. 46−2.31 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.90−1.76 (m, 2H), 1.56−1.40 (m, 1H), 0.97 (t, J = 7.1 Hz, 2H), 0.32 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) 170.7, 170.0, 138.4, 133.7, 129.2, 128.0, 90.3, 74.2, 72.1, 59.3, 42.7, 30.6, 28.2, 21.1, 21.0, 19.3, −2.3, −2.6. HRMS (ESI): $[M + H]^+$ $C_{20}H_{29}NO_5Si$ calcd 392.1893, found 392.1880. Anal. Calcd. for $C_{20}H_{29}NO_5Si$ (391.18): C 61.35, H 7.47, N 3.58. Found: C 61.31, H 7.45, N 3.48.

Acknowledgment. We thank the Cefipra program (no. 3605-E) for a Ph.D. grant to R.B. and the CNRS for the financial support. We also thank Dr. B. Kauffmann (IECB Bordeaux) for X-ray diffraction studies.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **8**, **9**, **11**, **12**, **14**, **21**, **22**, **24**, **25**, **26**, **27**, **28**, **31**, **32**, and **33** not described in the Experimental Section; copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.